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# Chemical Composition and Labeling of Substances Marketed as Selective Androgen Receptor Modulators and Sold via the Internet

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**IMPORTANCE** Recent reports have described the increasing use of nonsteroidal selective androgen receptor modulators, which have not been approved by the US Food and Drug Administration (FDA), to enhance appearance and performance. The composition and purity of such products is not known.

**OBJECTIVE** To determine the chemical identity and the amounts of ingredients in dietary supplements and products marketed and sold through the internet as selective androgen receptor modulators and compare the analyzed contents with product labels.

**DESIGN AND SETTING** Web-based searches were performed from February 18, 2016, to March 25, 2016, using the Google search engine on the Chrome and Internet Explorer web browsers to identify suppliers selling selective androgen receptor modulators. The products were purchased and the identities of the compounds and their amounts were determined from April to August 2016 using chain-of-custody and World Anti-Doping Association–approved analytical procedures. Analytical findings were compared against the label information.

**EXPOSURES** Products marketed and sold as selective androgen receptor modulators.

**MAIN OUTCOMES AND MEASURES** Chemical identities and the amount of ingredients in each product marketed and sold as selective androgen receptor modulators.

**RESULTS** Among 44 products marketed and sold as selective androgen receptor modulators, only 23 (52%) contained 1 or more selective androgen receptor modulators (Ostarine, LGD-4033, or Andarine). An additional 17 products (39%) contained another unapproved drug, including the growth hormone secretagogue ibutamoren, the peroxisome proliferator-activated receptor- $\delta$  agonist GW501516, and the Rev-Erba agonist SR9009. Of the 44 tested products, no active compound was detected in 4 (9%) and substances not listed on the label were contained in 11 (25%). In only 18 of the 44 products (41%), the amount of active compound in the product matched that listed on the label. The amount of the compounds listed on the label differed substantially from that found by analysis in 26 of 44 products (59%).

**CONCLUSIONS AND RELEVANCE** In this limited investigation involving chemical analyses of 44 products marketed as selective androgen receptor modulators and sold via the internet, most products contained unapproved drugs and substances. Only 52% contained selective androgen receptor modulators and many were inaccurately labeled.

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**A**nabolic steroids are the most frequently abused appearance- and performance-enhancing drugs.<sup>1-3</sup> Use of these drugs was largely limited to athletes prior to the 1980s, but since then use of these substances has increased among men with the goal of building muscle and appearing lean and muscular.<sup>1,3</sup> Selective androgen receptor modulators (ligands that bind to the androgen receptor and exert tissue-selective effects such as muscle growth<sup>4</sup>) have emerged as the new appearance- and performance-enhancing substances; however, the extent of product use is unknown. Several oral nonsteroidal selective androgen receptor modulators<sup>4,5</sup> are under development for treating functional limitations associated with aging or muscle wasting disorders, but none has been approved by the US Food and Drug Administration (FDA).

In response to reports of increased use of nonsteroidal selective androgen receptor modulators purchased through the internet by athletes, recreational bodybuilders, and members of the US armed forces,<sup>6,7</sup> a systematic investigation of the availability of products marketed as selective androgen receptor modulators through the internet was conducted. In addition, the chemical identity of the products sold as selective androgen receptor modulators and the amount of the compound in the product were determined by chemical analysis and compared with the label information.

## Methods

### Product Acquisition

Selective androgen receptor modulator products were found by conducting web-based searches from February 18, 2016, to March 25, 2016, using the Google search engine on the Chrome and Internet Explorer web browsers and the search terms *SARMs Supplements*, *SARMs*, *selective androgen receptor modulators*, and *buy*. The products purchased were typically supplied as capsules, tablets, or syrups in sealed containers.

### Chain-of-Sample Custody

From time of receipt, the product samples were subjected to rigorous chain-of-custody procedures similar to those used during acquisition of biological samples from athletes being tested for banned substances. Records of the chain of custody were maintained and the samples were stored in secured areas.

### Product Analyses

The products were tested between April 2016 and mid-August 2016. The extraction, screening, and confirmation (additional details appear in the [Supplement](#)) were performed using procedures<sup>8</sup> that have been approved by the World Anti-Doping Agency (WADA) for detecting the use of banned substances by athletes. Briefly, the equivalent of 1 serving of the product was extracted when that information was provided by the supplier; otherwise, 1 capsule or 1000  $\mu$ L of solution was extracted.

The product contents were subjected to both targeted and untargeted analysis. In the targeted analysis, the mass-spectrometric precursor to the fragment transitions specific to the compounds of interest were monitored at the known retention times for the compounds to provide the highest de-

## Key Points

**Question** What types and quantity of ingredients are found in products sold through the internet and advertised to contain selective androgen receptor modulators?

**Findings** Chemical analyses of 44 products sold via the internet as selective androgen receptor modulators revealed that only 52% contained selective androgen receptor modulators and another 39% contained another unapproved drug. In addition, 25% of products contained substances not listed on the label, 9% did not contain an active substance, and 59% contained substance amounts that differed from the label.

**Meaning** Selective androgen receptor modulators, which have not been approved by the US Food and Drug Administration, were available through the internet and were inaccurately labeled.

gree of sensitivity in detecting their presence. In the untargeted analysis, full mass-spectrometric scans were acquired with and without molecular fragmentation across the full chromatogram to allow detection of all ionizing species (ie, without predefining which molecular masses to identify). The mass-spectrometric data were acquired with high mass accuracy (mass error of <10 ppm) and at high resolution (35 000 Da) to enable determination of the candidate molecular formulas for the detected masses.

Initially, the compounds were tested using general-purpose screenings meeting all the requirements set forth by WADA for detecting the use of performance-enhancing drugs by athletes.<sup>9</sup> If no banned substances were detected in the general-purpose screening, further analyses were performed using untargeted screenings as described above. The use of general-purpose screening procedures enabled detection of additional performance-enhancing drugs other than selective androgen receptor modulators.

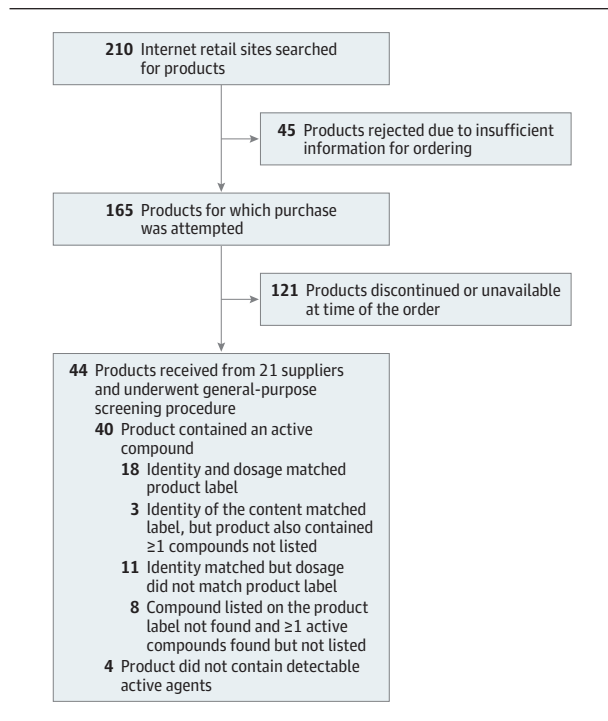
When the screening analysis revealed a selective androgen receptor modulator or another performance-enhancing substance, the findings were confirmed by more specific methods and reference materials for comparison of the characteristics from mass-spectral fragmentation. WADA-specified criteria were used for positive identification of compounds.<sup>8,9</sup> The amount of compound was estimated based on comparison of the response with those obtained from standards containing known quantities.

The analytical methods have an estimated intra-assay coefficient of variation of 20% and an interassay coefficient of variation of 20%. Label claims were considered to match the experimentally measured values when they were within the estimated uncertainty windows of the analyses. We compared the compounds found in the product and their amounts with the product label.

## Results

Internet searches yielded 210 products from 51 supplier sites offering selective androgen receptor modulators and other muscle-building compounds (**Figure 1**). Of these, 45 products

Figure 1. Flow of Tested Products Through the Systematic Search and Analytical Process



could not be purchased due to insufficient information on the websites, and 121 products could not be obtained because they were out of stock, discontinued, or had other restrictions. Forty-four products purchased from 21 suppliers were analyzed (Figure 2 and Table). The number of products purchased from various suppliers ranged from 1 to 5.

Some companies used the term *SARM* in their product label or in advertising, even though the product was not a selective androgen receptor modulator (eg, growth hormone secretagogue ibutamoren) (Figure 2). Of the 44 purchased products, the following compounds were listed on the labels: Ostarine (also known as enobosarm, GTx-024, MK-2866, S-22, and S22), Andarine (also known as GTx-007), LGD-4033 (also known as Ligandrol), RAD140 (also known as Testolone), ibutamoren (also known as MK-677, L163,191), GW501516 (also known as Cardarine, Endurobol, GSK-516, and GW1516), and SR9009 (also known as Stenabolic).

Figure 2 shows the most common compounds detected in the 44 products. Selective androgen receptor modulators, peroxisome proliferator-activated receptor- $\delta$  (PPAR- $\delta$ ) agonists, and growth hormone secretagogues were the 3 most frequently found classes of compounds among those tested. Selective androgen receptor modulators accounted for 23 of the 44 tested compounds (52%). Ostarine and LGD-4033 were found in more than 80% of selective androgen receptor modulator products. The PPAR- $\delta$  agonist GW501516 was the second most frequently found compound, and the growth hormone secretagogue ibutamoren was the third most common.

In only 18 of the 44 products (41%), the amount of active compound in the product matched that listed on the label.

In 11 products (25%), the listed compound was detected, but in an amount that differed from the label (Table and Figure 1). In 8 products (18%), the compound listed on the label was not found; however, different compounds not listed on the label were found. Three products (7%) contained the amount listed on the label but also contained an additional compound not listed. Four products contained minimal amounts of the selective estrogen receptor modulator tamoxifen. In another 4 products (9%), no active compounds were detected.

The amount of the compounds listed on the label differed substantially from that found by analysis in 26 of 44 products (59%). Seventeen products (39%) contained another unapproved drug, including the growth hormone secretagogue ibutamoren, the peroxisome proliferator-activated receptor- $\delta$  agonist GW501516, and the Rev-Erba agonist SR9009. None of the 5 products purchased from 1 supplier contained the compounds listed on the label (Table). In 2 of 5 products obtained from this supplier, the analyses detected banned substances not listed on the label.

Of the 44 products, 20 (45%) were sold as dietary supplements and contained Supplement Fact panels on their labels. No product label included a Drug Fact panel. There were 24 products (55%) labeled as being for research use only, not for human consumption, or both (Table). The retail cost, product form (capsules or solution), and contents (quantity or solution volume) appear in the Table.

## Discussion

This limited investigation found that products containing investigational selective androgen receptor modulators and other performance-enhancing drugs not approved by the FDA can be purchased from internet sites without a prescription. Although the tested products were advertised as selective androgen receptor modulators, some products contained growth hormone secretagogues,<sup>10</sup> PPAR- $\delta$  agonists,<sup>11</sup> and Rev-Erba agonists,<sup>12</sup> all of which are recognized by WADA as banned substances.<sup>13</sup> Neither the efficacy nor the safety of these investigational drugs has been demonstrated. For many products, the ingredients and their amounts found in these analyses did not match the label information. These findings suggest the need for greater regulatory oversight of products sold on the internet.

Most tested products were investigational drugs that have not received FDA approval. The FDA requires all drugs to have an approved application for continued marketing.<sup>14,15</sup> Such approval from the FDA requires demonstration of safety and efficacy.<sup>15</sup> Some compounds such as Ostarine,<sup>16</sup> Andarine, LGD4033,<sup>6</sup> and ibutamoren<sup>10</sup> have undergone some human studies, but have not received FDA approval. The development of GW501516<sup>17</sup> was halted because of safety concerns. Preclinical studies have occurred for SR9009, but no human trials. Internet sales of drugs that are not approved by the FDA and whose benefits and safety have not been demonstrated raise public safety concerns. Individuals who use these products generally do not disclose the use of these products to their physicians; furthermore, clinicians

Figure 2. Pharmacological Classes of Appearance and Performance Enhancing Substances Found in the Search

Compound	Chemical Structure	Modes of Action	Synonyms
Ostarine		SARM	Enobosarm <sup>a</sup> ; GTX-024; MK-2866; S-22; (2S)-3-(4-cyanophenoxy)-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide
Andarine		SARM	Andarine <sup>a</sup> ; GTX-007
LGD-4033		SARM	Ligandrol <sup>a</sup> ; 4-((R)-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)-2-trifluoromethylbenzonitrile
RAD140		SARM	Testolone <sup>a</sup> ; 2-chloro-4-((1R,2S)-1-(5-(4-cyanophenyl)-1,3,4-oxadiazol-2-yl)-2-hydroxypropylamino)-3-methylbenzonitrile
SR9009		Rev-Erba agonist	Stenabolic <sup>a</sup> ; ethyl-3-(((4-chlorobenzyl)((5-nitrothiophen-2-yl)methyl)amino)methyl)pyrrolidine-1-carboxylate
Ibutamoren		Growth hormone secretagogue	MK-677; L163,191; R-1'-(2-methylalanyl-O-benzyl-D-seryl)-1-methylsulfonyl-1,2-dihydrospiro[indole-3,4'-piperidine]
GW501516		PPARδ agonist	Cardarine <sup>a</sup> ; Endurobol <sup>a</sup> ; GSK-516; GW1516; 4-(((4-methyl-2-(4-(trifluoromethyl)phenyl)-1,3-thiazol-5-yl)methyl)sulfonyl)-2-methylphenoxy)acetic acid

SARM indicates selective androgen receptor modulator; and PPAR-δ, peroxisome proliferator-activated receptor-δ.

<sup>a</sup> Indicates trade name.

do not have ready access to information about the contents and safety of such unapproved products, further increasing the health risk to the user.

The Fair Packaging and Labeling Act<sup>14</sup> requires consumer products to be labeled to disclose the contents and the product identity.<sup>8</sup> For drugs, a listing of drug facts with potential adverse effects and guidelines for safe use are required.<sup>18</sup> Of the products tested, some did not contain the compound listed on the label and others contained amounts that differed substantially from the label. Nearly one-quarter of tested products contained compounds not included on the label, and some included a mixture of 2 or more compounds.

Nearly half the products were marketed as dietary supplements. The FDA defines dietary supplements as products taken by mouth that contain a “dietary ingredient” such as vitamins, minerals, amino acids, and herbs or botanicals that can be used to supplement the diet.<sup>19</sup> None of the tested compounds meets the definition of a dietary supplement.

Antidoping agencies have identified cases of doping with selective androgen receptor modulators by athletes.<sup>20</sup>

Contamination of dietary supplements by anabolic steroids also has been reported.<sup>21</sup> This investigation demonstrates the ease with which unapproved appearance- and performance-enhancing drugs can be purchased over the internet, which could increase abuse by adolescents, military personnel, and recreational weightlifters.

In addition, the ability of small laboratories located inside and outside the United States to synthesize and package pharmaceutical agents has contributed to the ease of global purchasing of these compounds. Vendors easily disseminate information about the products to potential users via the internet. The ease of website creation makes it possible for suppliers to create and remove websites as often as needed to stay ahead of law enforcement, regulators, and posted reviews from users who experienced adverse effects.

This investigation has several strengths. Rigorous testing procedures, which are similar to those used to detect banned substances in the WADA-certified testing program, were used for the analyses of these compounds. The chain of custody was recorded and products were stored in secure locations. The sen-

Table. Products, Suppliers, Labeling, and Chemical Testing of 44 Products Sold as Selective Androgen Receptor Modulators via the Internet

Product ID <sup>a</sup>	Supplier ID <sup>b</sup>	Label Information for Use	Form and Product Contents	Retail Cost, \$	Label Claims	Findings
<b>Identity and Dosage Match</b>						
337083	C	Not for human consumption; Research use only	60 capsules	89.99	10 mg of GW501516 per capsule	10-50 mg of GW501516 per capsule
337232	F		240 capsules	64.99	5 mg of Andarine per capsule	1-10 mg of Andarine per capsule
337235	H		90 capsules	44.99	4 mg of LGD-4033 per capsule	1-5 mg of LGD-4033 per capsule
337236	H		90 capsules	69.95	10 mg of ibutamoren per capsule	5-20 mg of ibutamoren per capsule
337238	I	Research use only	30-mL solution	196.59	25 mg/mL of ibutamoren	10-50 mg/mL of ibutamoren
337395	J		30 tablets	74.99	15 mg of LGD-4033 per tablet	5-20 mg of LGD-4033 per tablet
337396	F		90 capsules	59.99	10 mg of Ostarine per capsule	1-5 mg of Ostarine per capsule
342066	K		90 capsules	59.95	11 mg of GW501516 per capsule	10-20 mg of GW501516 per capsule
342067	K		90 capsules	59.95	6 mg of LGD-4033 per capsule	1-10 mg of LGD-4033 per capsule
342068	K		90 capsules	59.95	12 mg of Ostarine per capsule	1-10 mg of Ostarine per capsule
342069	L		90 capsules	70.00	20 mg of Ostarine per capsule	10-20 mg of Ostarine per capsule
342075	N		120 capsules	64.95	12.5 mg of Ostarine per capsule	10-20 mg of Ostarine per capsule
342076	O		90 capsules	54.95	10 mg of Ostarine per capsule	5-10 mg of Ostarine per capsule
342077	O		60 capsules	79.95	12.5 mg of ibutamoren per capsule	10-20 mg of ibutamoren per capsule
342078	O		90 capsules	69.95	5 mg of LGD-4033 per capsule	1-10 mg of LGD-4033 per capsule
342952	T	Not for human consumption; Research use only	30-mL solution	99.99	10 mg/mL of RAD140	Formula match for RAD140
342953	T	Not for human consumption; Research use only	30-mL solution	59.99	10 mg/mL of GW501516	10-50 mg/mL of GW501516
342954	T	Not for human consumption; Research use only	30-mL solution	99.99	25 mg/mL of ibutamoren	20-80 mg/mL of ibutamoren
<b>Identity Matches Label but Additional Compounds Found</b>						
342082	R	Not for human consumption; Research use only	60-mL solution	119.99	20 mg/mL of GW501516	10-50 mg/mL of GW501516, <0.1 mg/mL of tamoxifen
342086	R	Not for human consumption; Research use only	60-mL solution	119.99	50 mg/mL of Andarine	10-50 mg/mL of Andarine, <0.1 mg/mL of tamoxifen
342089	S	Research use only	2 capsules	Free sample	10 mg of ibutamoren per capsule	10-20 mg of ibutamoren per capsule, <0.1 mg of GW501516 per capsule
<b>Identity Match but Dosage Does not Match</b>						
336800	A	Not for human consumption; Research use only	60 capsules	109.99	25 mg of Ostarine per capsule	1-5 mg of Ostarine per capsule
336801	B	Not for human consumption; Research use only	90 capsules	59.95	10 mg of GW501516 per capsule	0.1-1 mg of GW501516 per capsule
337084	D		120 capsules	49.99	25 mg of Ostarine per capsule	1-5 mg of Ostarine per capsule
337233	G		90 capsules	69.99	12.5 mg of Ostarine per capsule	1-5 mg of Ostarine per capsule
342079	P	Not for human consumption	90 capsules	59.95	20 mg of Ostarine per capsule	1-5 mg of Ostarine per capsule
342080	F	Not for human consumption; Research use only	180 capsules	63.95	5 mg of GW501516 per capsule	0.1-1 mg of GW501516 per capsule
342083	R	Not for human consumption; Research use only	60-mL solution	159.99	50 mg/mL of ibutamoren	10-20 mg/mL of ibutamoren
342085	R	Not for human consumption; Research use only	60-mL solution	129.99	30 mg/mL of LGD-4033	1-10 mg/mL of LGD-4033
342088	S		90 capsules	54.99	5 mg of GW501516 per capsule	10-20 mg of GW501516 per capsule
342950	T	Not for human consumption; Research use only	30-mL solution	54.99	10 mg/mL of LGD-4033	0.1-1 mg/mL of LGD-4033
342951	T	Not for human consumption; Research use only	30-mL solution	44.99	50 mg/mL of Andarine	10-20 mg/mL of Andarine

(continued)

Table. Products, Suppliers, Labeling, and Chemical Testing of 44 Products Sold as Selective Androgen Receptor Modulators via the Internet (continued)

Product ID <sup>a</sup>	Supplier ID <sup>b</sup>	Label Information for Use	Form and Product Contents	Retail Cost, \$	Label Claims	Findings
<b>Compound on Label not Found but Unlisted Active Compounds Found</b>						
337231	E		90 capsules	59.95	8 mg of Ostarine, 6 mg of GW501516, 35 mg of 5-aminoimidazole-4-carboxamide ribonucleotide per capsule	0.1-1 mg of Ostarine per capsule, 1-5 mg of androstatrienedione per capsule
337237	I	Research use only	30-mL solution	179.49	50 mg/mL of Ostarine	0.1-1 mg/mL of Ostarine, 10-50 mg/mL of Andarine, <0.1 mg/mL of GW501516
337394	C	Not for human consumption; Research use only	90 capsules	119.99	3 mg of RAD140 per capsule	2.1 mg of Ostarine, <0.1 mg of Andarine per capsule
342072	M	Not for human consumption; Research use only	40 capsules	62.99	20 mg of SR9009 per capsule	1-5 mg of androstatrienedione per capsule
342073	M	Not for human consumption; Research use only	40 capsules	61.99	30 mg of ibutamoren per capsule	1-5 mg of LGD-4033 per capsule
342081	Q		60-mL solution	159.99	20 mg/mL of LGD-4033, 25 mg/mL of Ostarine, 20 mg/mL of ibutamoren	1-10 mg/mL of LGD-4033, 1-10 mg/mL of GW501516, 1-5 mg/mL of ibutamoren, <0.1 mg/mL of tamoxifen
342084	R	Not for human consumption; Research use only	60-mL solution	129.99	50 mg/mL of Ostarine	10-50 mg/mL of GW501516, <0.1 mg/mL of tamoxifen, <0.1 mg/mL of Ostarine
342955	U		60 capsules	60.00	20-mg blend of Ostarine and GW501516 per capsule	5-10 mg of Ostarine, 5-10 mg of LGD-4033 per capsule
<b>No Active Agents Detected in Product</b>						
337234	F		90 capsules	39.95	5 mg of LGD-4033 per capsule	No active agents detected
342070	M	Not for human consumption; Research use only	40 capsules	54.99	25 mg of Ostarine per capsule	No active agents detected
342071	M	Not for human consumption; Research use only	40 capsules	62.99	70 mg of 5α-hydroxylaxogenin per capsule	No active agents detected
342074	M	Not for human consumption; Research use only	40 capsules	59.99	15 mg of RAD140 per capsule	No active agents detected

<sup>a</sup> Internal laboratory identifier.

<sup>b</sup> Coded indicator of the company the product was branded under.

sitivity of these procedures enabled detection of even small quantities of compounds.

**Limitations**

This study has several limitations. Because all possible internet sites were not searched, this search should not be viewed as exhaustive. It is possible that additional appearance- and performance-enhancing substances are being sold on the internet as selective androgen receptor modulators. The results apply only to the products purchased. Therefore, these findings should not be viewed as representative of all products sold through internet sites because the sample is limited

to a single point in purchase time. Because of the rapidly changing nature of such internet sites, the results of similar searches will vary.

**Conclusions**

In this limited investigation involving chemical analyses of 44 products marketed as selective androgen receptor modulators and sold via the internet, most products contained unapproved drugs and substances. Only 52% contained selective androgen receptor modulators and many were inaccurately labeled.

**ARTICLE INFORMATION**

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**Correction:** This article was corrected on February 20, 2018, to add conflict of interest disclosures to the existing disclosures for Dr Bhasin.

**Author Contributions:** Drs Van Wagoner and D. Eichner had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:**

Van Wagoner, A. Eichner, Bhasin, D. Eichner.

**Drafting of the manuscript:** All authors.

**Critical revision of the manuscript for important**

**intellectual content:** Van Wagoner, A. Eichner, Bhasin, D. Eichner.

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and as this committee's chair from 2011 to 2015. No other disclosures were reported.

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